SYNTHESIS OF NOVEL SUBSTITUTED [1,2,4]TRIAZOLO[1,5-*a*]PYRIDINES AND THEIR RELATED PYRANO[2,3-*d*]IMIDAZOLE DERIVATIVS

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Abstract

Synthesis of the diaminopyridine derivatives **3** and **4** from 2-cyanoacetohydrazide **1** was described. The [1,2,4]triazolo[1,5-a]pyridine derivatives **10, 11** and **13-15** were obtained by reaction of **3** with ethyl chloroformate/DMF reagent mixture, acetic anhydride, triethyl orthoformate, -orthoacetate or aromatic aldehydes. Deamination of **3** to the aminopyridine derivatives **17** was carried out. The triazolopyridine derivatives **11** were obtained also in one step synthesis from **2** and N′-acetyl-2-cyanoacetohydrazide **19**. Condensation of the thiohydantion **20** with **2** gave pyrano[2,3-*d*]imidazoles **24**.

Introduction

Pyridines have been reported as biologically interesting molecules[1-4] and precursors for the synthesis of triazolo[1,5-*a*]pyridines. Several methods have previously described the synthesis of triazolo[1,5-*a*]pyridines from 1,6-diaminopyridines.[5-11] Moreover, triazolo[1,5-*a*]pyridine systems are reported to be useful compounds as pharmaceuticals,[12] fluorescent brighteners,[13] complexing agents,[14] herbicides,[15] cyan dye mixture for thermal color proofing,[16] and as jet-printing ink[17,18] agents. Recently, derivatives of this ring system are prepared from N′-arylmethylidene-2-cyanohydrazide.[19] Triazolo[1,5-*a*]pyridines have also been prepared by ring transformation of triazolo[4,3-*a*]pyridine[20] and from 2-thioxopyrones.[21]

In the present investigation the synthesis of some novel substituted triazolo[1,5-*a*]-pyridines and their related pyrano[2,3-*d*]imidazole derivatives was attempted for their expected useful biological properties.

Results and Discussion

Reaction of 2-cyanoacetohydrazide **1** with (2-furylmethylene)malononitrile **2a**[22] in ethanol afforded 1,6-diamino-4-(2-furyl)-2-oxo-1,2-dihydropyridine-3,5-dicarbonitrile

3a (previously reported without data).[23] The 1,2,3,4-tetrahydropyridine-3,5-dicarbonitrile derivative **4** was also isolated (Scheme 1). Dehydrogenation of product **4** to **3a** was carried out using *o*-chloranile at room temperature.

Structure of **4** was confirmed by careful analysis of its spectral data. Its ^{1}H-NMR spectrum revealed characteristic signals at δ 4.23 ppm (d, *J* 6.4 Hz) and 5.09 ppm (d, *J* 6.4 Hz) for C_4-H and C_3-H of the pyridine ring, respectively. Moreover, its EI-MS spectrum showed molecular ion peak (M^+) at *m/z* 243 (100%).

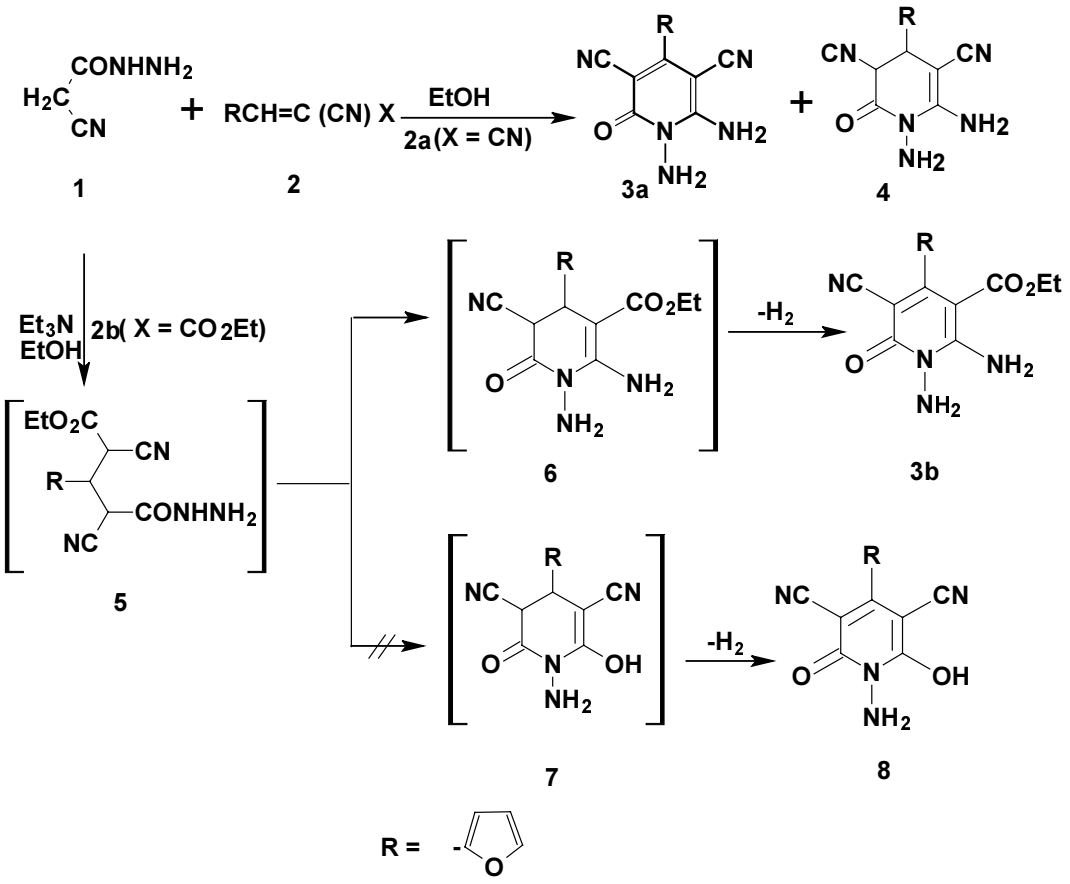
Upon carrying out the reaction of **1** with ethyl (*E*)-2-cyano-3-(2-furyl)acrylate **2b**[24] without catalyst no products could be isolated. Whereas, reaction of **1** with **2b** in the presence of triethylamine afforded smoothly 1,2-diamino-6-oxo-1,6-dihydro-pyridine-3-carboxylate **3b** rather than 6-hydroxypyridine-3,5-dicarbonitrile derivative **8** (Scheme 1).

Cyclization of products **3a** and **3b** with ethyl chloroformate/N,N-dimethyl-formamide reagent mixture[25] (which has been previously reported for cyclization of *o*-amino heterocyclic carboxamides to their condensed pyrimidinone derivatives) yielded 7-(2-furyl)-5-oxo-3,5-dihydro[1,2,4]triazolo[1,5-*a*]pyridine-6,8-dicarbonitrile (**10a**) and ethyl 6-cyano-7-(2-furyl)-5-oxo-3,5-dihydro[1,2,4]triazolo[1,5-*a*]pyridine-8-carboxylate (**10b**), respectively (Scheme 2).

When compound **3a** was allowed to react with acetic anhydride two products were formed. Based on their elemental analyses and spectral data (IR, ^{1}H NMR and MS) these were identified as 7-(2-furyl)-2-methyl-5-oxo-3,5-dihydro[1,2,4]triazolo[1,5-*a*]pyridine-6,8-dicarbonitrile (**11a**) and N-acetyl-N-[6-(acetylamino)-3,5-dicyano-4-(2-furyl)-2-oxopyridin-1(2*H*)-yl]acetamide (**12**). Under the same reaction conditions the reaction of **3b** with acetic anhydride afforded ethyl 2-methyl-3,5-dihydro[1,2,4]triazolo[1,5-*a*]-pyridine-8-carboxylate (**11b**) as the sole product (Scheme 2).

Unexpectedly, upon reacting the pyridine derivatives **3** with either triethyl orthoformate or triethyl orthoacetate in acetonitrile, 3-ethyl-7-(2-furyl)-5-oxo-3,5-dihydro[1,2,4]triazolo[1,5-*a*]pyridine-6,8-dicarbonitriles **13a** and **13b** and ethyl 6-cyano-3-ethyl-7-(2-furyl)-5-oxo-3,5-dihydro[1,2,4]triazolo[1,5-*a*]pyridine-8-carboxylates **13c** and **13d** were smoothly obtained, rather than the expected products of types **10** and **11** (Scheme 2). ^{1}H NMR spectra of **13** revealed the characteristic N-ethyl proton signals at δ 1.43–1.54 (triplet) and 4.42–4.87 (quartet) ppm for CH_3 and CH_2, respectively.

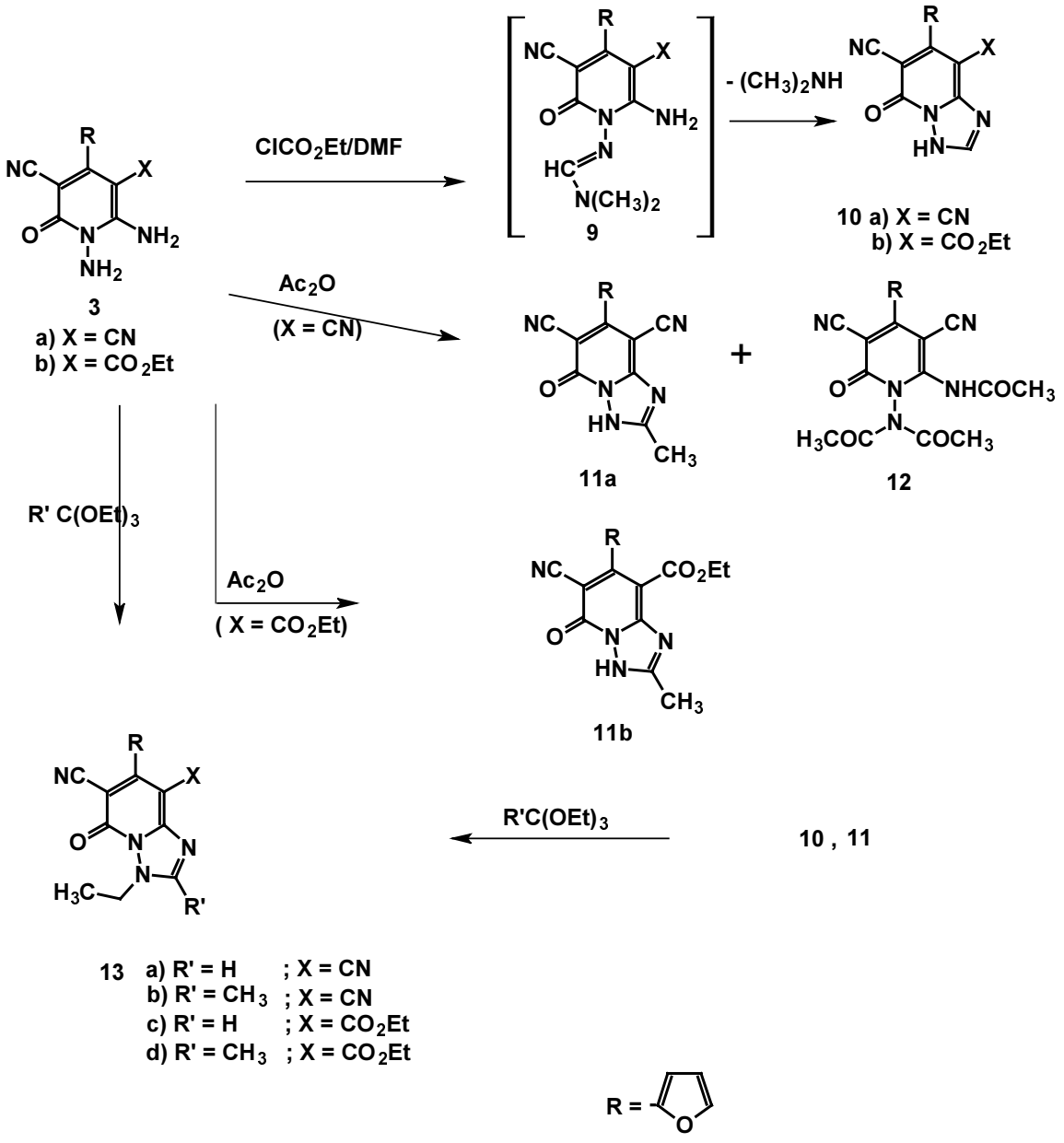
Scheme 1



The structure of compounds **13** was also chemically elucidated. Thus, by reaction of products **10** and **11** with either triethyl orthoformate or triethyl orthoacetate the corresponding 3-ethyl-triazolo[1,5-*a*]pyridine derivatives **13a-d** were obtained. Therefore, in the present investigation triethyl orthoformate and triethyl orthoacetate are applied as cyclizing and alkylating agents in the same time.

Reaction of products **3a** and **3b** with *p*-fluorobenzaldehyde or salicylaldehyde in dioxane containing piperidine as the catalyst afforded unexpected products piperidinium 2-aryl-7-(2-furyl)-5-oxo-3,5-dihydro[1,2,4]triazolo[1,5-*a*]pyridine-6,8-dicarbonitriles **14a** and **14b** and piperidinium ethyl 2-aryl-6-cyano-7-(2-furyl)-5-oxo-3,5-dihydro [1,2,4]-triazolo[1,5-*a*]pyridine-8-carboxylates **14c** and **14d**, respectively in good yield (Scheme 3). The structure of **14** was elucidated from the analytical and ^{1}H NMR spectral data. The latter show signals at δ 1.61 ppm and 3.02 ppm that have been assigned to the piperidinium cation. The piperidinium salts **14a-d** were formed by formation of a piperidinium cation and a triazole anion[26] as shown in Scheme 3.

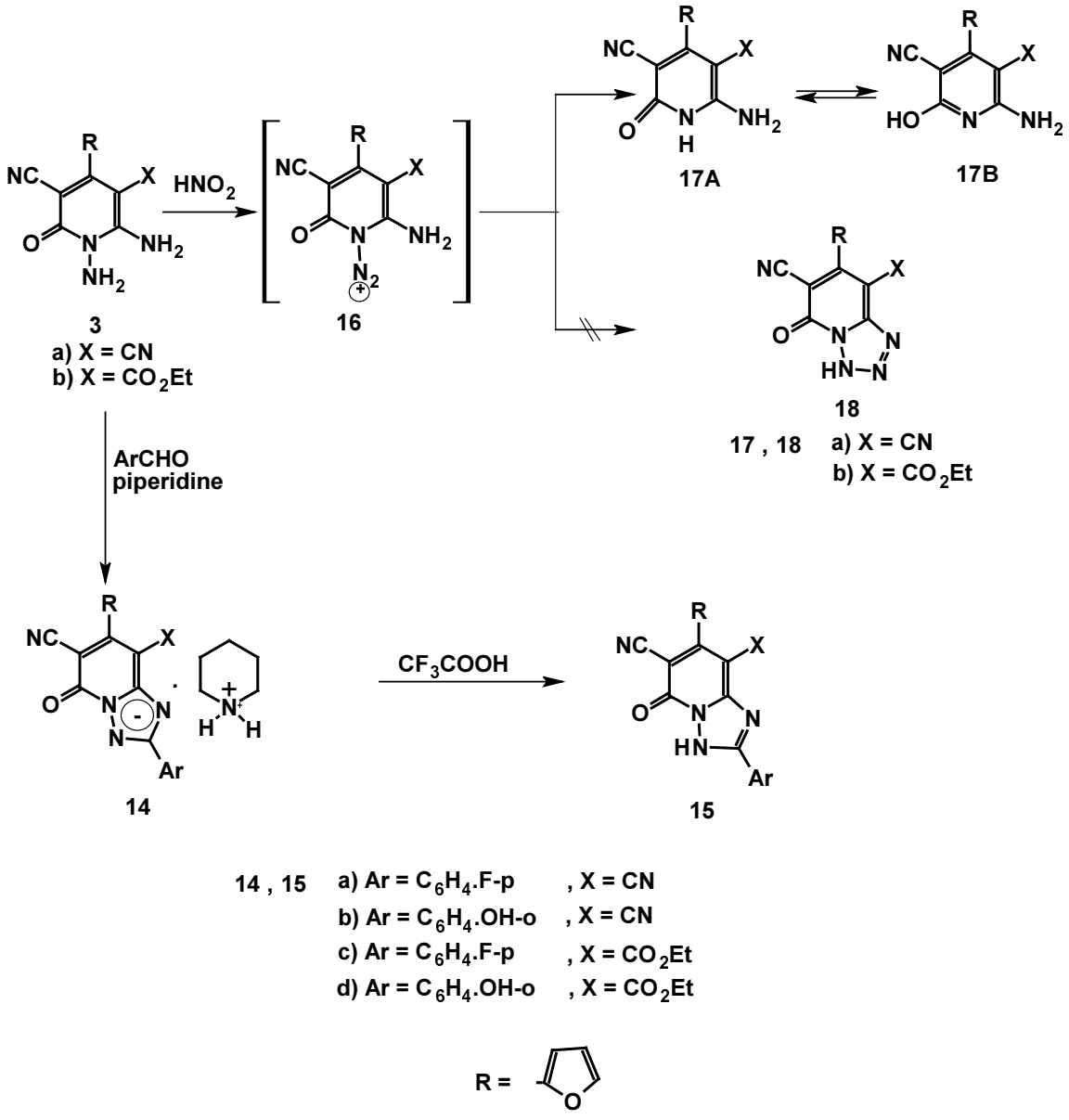
Scheme 2



The dequarternized triazolo[1,5-*a*]pyridine derivatives **15** were obtained by treating products **14** with trifluoroacetic acid at room temperature. ^{1}H NMR spectra of **15** revealed the absence of the piperidine proton signals. Also, their mass spectra showed the absence of piperidine fragment peak at *m/z* 84.

N-Deamination of the diaminopyridine derivatives **3a** and **3b** was also carried out under mild conditions. Thus, upon treating products **3a** and **3b** with sodium nitrite in aqueous acetic acid, the unexpected 6-amino-2-oxo-1,2-dihydropyridine-3,5-

Scheme 3



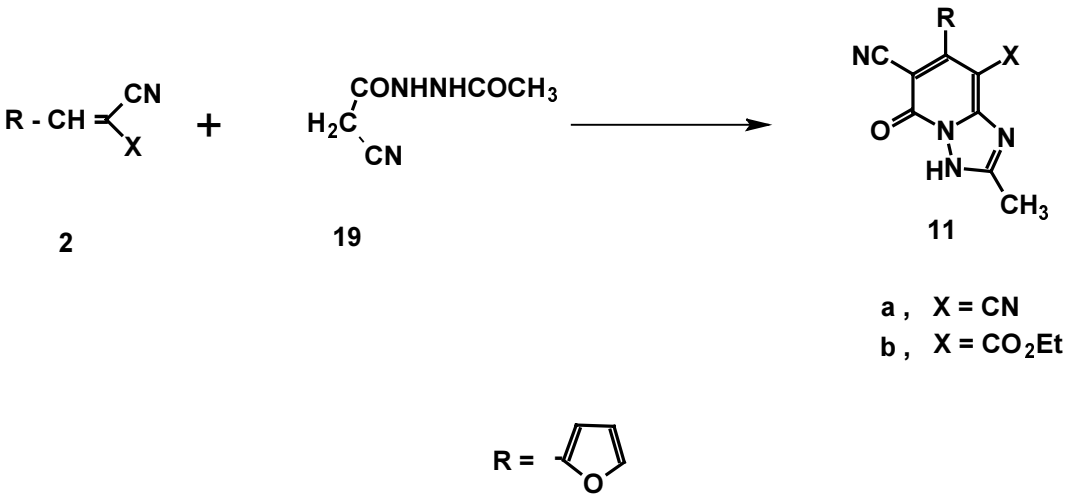
dicarbonitrile **17a** and ethyl 2-amino-5-cyano-6-oxo-1,6-dihydropyridine-3-carboxylate **17b** were obtained respectively, rather than the expected tetrazolopyridine derivatives **18** (Scheme 3). It worth mentioning that the product **17a** has been previously synthesized, although in a relatively low yield, from 4-(2-furyl)-3,5-dicyano-2(1*H*)pyridine-selenones.[27]

Elemental analysis and spectral data confirmed the proposed structure of **17b**. Its IR spectrum (KBr) showed stretching vibration bands for NH and C=O around 3441-

3291 and at 1694 ($COOC_2H_5$) and 1650 cm^{-1}, respectively, (characteristic for pyridone system). On the other hand IR spectrum of **17b** in DMSO showed no carbonyl stretching vibrations around 1650 cm^{-1}. ^1H NMR spectrum of **17b** exhibits proton signal at δ 11.66 ppm (down-field shifted), which could be assigned to iminolic form[6b] **17B**. Mass spectrum with M^+ at *m/z* 273 (100%) is also in a good agreement with the proposed structure of **17b**.

One step synthesis of the triazolo[1,5-*a*]pyridine derivatives **11a** and **11b** was also attempted in the present work. Thus when N′-acetyl-2-cyanoacetohydrazide **19** was heated under reflux in ethanol, containing triethylamine as a catalyst, and unsaturated nitriles **2**, the corresponding triazolopyridine derivatives **11a** and **11b** were obtained in somewhat low yield (30% for **11a**, 40% for **11b**) with respect to a previously reported mechanism[28] (Scheme 4).

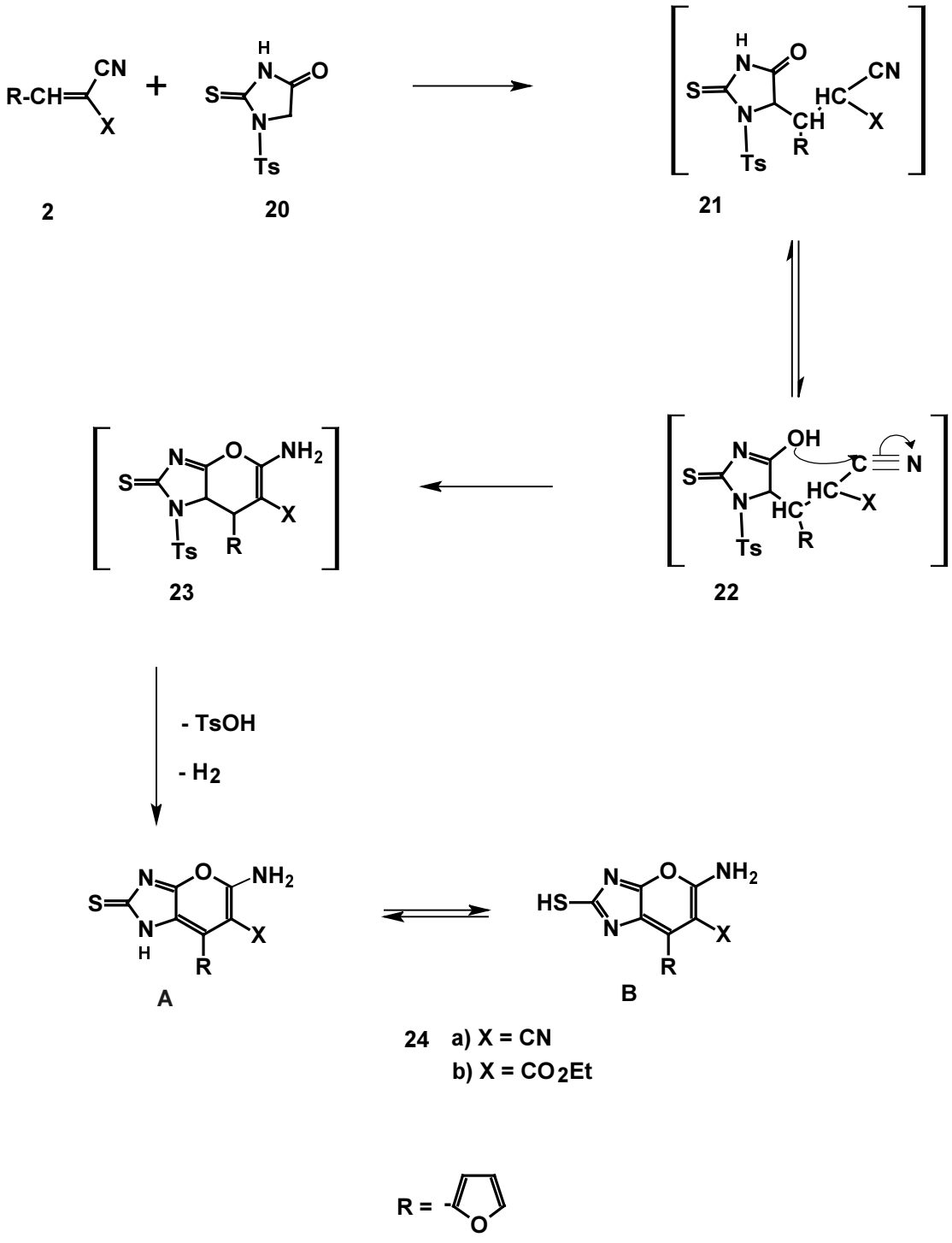
Scheme 4



The present work was extended to investigate condensation of **2** with the thiohydantion derivative **20**.[29] This reaction produced the fused ring system of pyrano[2,3-*d*]imidazole derivatives **24** when carried out in the presence of triethyl amine (Scheme 5). This condensation reaction may initially start with addition of the active methylene group of **20** to the olefinic double bond of **2** giving rise to Michael adduct **21**, followed by rearrangement and cyclization to **23**. The latter intermediate gave the more stable 5-amino-7-(2-furyl)-2-thioxo-1,2-dihydropyrano[2,3-*d*]imidazole-6-carbonitrile

24a and ethyl 5-amino-7-(2-furyl)-2-thioxo-1,2-dihydropyrano[2,3-*d*]imidazole-6-carboxylate **24b** upon loosing *p*-toluenesulfonic acid and a molecule of hydrogen (Scheme 5).

Scheme 5



IR spectra of products **24** (KBr) revealed NH and C=S vibrations in the region of 3435-3200 and 1241-1220 cm^{-1}, respectively. On the other hand, the IR spectra in DMSO lack the C=S stretching vibrations. ^1H NMR spectra of products **24** lack the presence of CH_2 and tolyl groups, but revealed the other expected characteristic signals. Also, it was noticed that the HN-C=S proton signals were down-field shifted and appeared in δ 12.83-12.95 ppm region. This shift can be attributed to the thiol form **24B** in solution. Mass spectra of **24a** and **24b** showed a molecular ion peak (M^+) at *m/z* 258 (in a relative intensity of 56.39%) and *m/z* 305 (in a relative intensity of 87.50%), respectively.

Table 1. Characterization of the synthesized compounds.

Cmpd	Mp (°C) (Solvent)	Yield (%) r. time	Mol. Formula (Mol. Wt.)	Analysis Calcd/Found (%) C	H	N
3a	310-12 (n-butanol)	60	$C_{11}H_7N_5O_2$ (241.21)	54.77 54.78	2.93 3.03	29.04 29.28
3b	198-200 (EtOH)	60	$C_{13}H_{12}N_4O_4$ (288.26)	54.16 54.27	4.20 4.28	19.44 19.59
4	195-6 (EtOH)	13	$C_{11}H_9N_5O_2$ (243.22)	54.32 54.42	3.73 3.87	28.80 28.70
10a	274-6 (EtOH/DMF)	86	$C_{12}H_5N_5O_2$ (251.20)	57.37 57.43	2.01 2.00	27.88 28.00
10b	288-90 (Acetonitrile)	77	$C_{14}H_{10}N_4O_4$ (298.25)	56.38 56.10	3.38 3.38	18.79 19.00
11a	306-8 (Acetonitrile)	33	$C_{13}H_7N_5O_2$ (265.23)	58.87 58.68	2.66 2.92	26.41 26.49
11b	291-3 (n-butanol)	57	$C_{15}H_{12}N_4O_4$ (312.28)	57.69 58.03	3.87 4.00	17.94 17.99
12	275-7 (MeOH)	15	$C_{17}H_{13}N_5O_5$ (367.31)	55.59 55.70	3.57 3.50	19.07 19.30
13a	266-8 (EtOH/DMF)	65 10 h	$C_{14}H_9N_5O_2$ (279.25)	60.21 60.03	3.25 3.40	25.08 24.81
13b	271-3 (Acetonitrile)	60 5 h	$C_{15}H_{11}N_5O_2$ (293.28)	61.43 61.48	3.78 4.00	23.88 24.13
13c	269-71 (EtOH)	70 10 h	$C_{16}H_{14}N_4O_4$ (326.26)	58.89 59.00	4.32 4.40	17.17 17.00
13d	240-2 (EtOH)	64 5 h	$C_{17}H_{16}N_4O_4$ (340.33)	59.99 60.10	4.74 4.70	16.46 16.50
14a	344-6 (Acetonitrile/DMF)	74	$C_{23}H_{19}FN_6O_2$ (430.43)	64.18 64.26	4.45 4.52	19.53 19.78

Table 1. *Continued on the next page.*

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14b	302-4 (Acetonitrile)	69	$C_{23}H_{20}N_6O_3$ (428.44)	64.47 64.41	4.71 4.94	19.62 19.45
14c	221-2 (MeOH)	54	$C_{25}H_{24}FN_5O_4$ (477.48)	62.88 63.00	5.07 4.90	14.67 14.80
14d	225-6 (MeOH)	52	$C_{25}H_{25}N_5O_5$ (475.49)	63.15 63.00	5.30 5.40	14.73 14.80
15a	348-50 (Acetonitrile/DMF)	81	$C_{18}H_8FN_5O_2$ (345.28)	62.61 62.80	2.34 2.50	20.28 20.00
15b	342-4 (Acetonitrile)	81	$C_{18}H_9N_5O_3$ (343.29)	62.97 63.10	2.64 2.50	20.40 20.60
15c	303-5 (MeOH)	74	$C_{20}H_{13}FN_4O_4$ (392.33)	61.22 61.40	3.34 3.50	14.28 14.20
15d	286-8 (MeOH)	79	$C_{20}H_{14}N_4O_5$ (390.34)	61.54 61.70	3.61 3.50	14.35 14.50
17b	303-5 (EtOH)	78	$C_{13}H_{11}N_3O_4$ (273.24)	57.14 57.21	4.06 4.25	15.38 15.51
24a	313-5 (Acetonitrile/DMF)	52 5 h	$C_{11}H_6N_4O_2S$ (258.25)	51.16 51.26	2.34 2.39	21.70 21.99
24b	241-3 (EtOH)	48 10 h	$C_{13}H_{11}N_3O_4S$ (305.30)	51.14 51.21	3.63 3.90	13.76 13.49

Table 2. Spectral determinations for the synthesized products.

	IR (KBr) cm^{-1}				^1H NMR (DMSO-d_6)*	MS
Cmpd	υNH	υCN	υCO	υCS	δ ppm	*m/z*
3a	3400 3280 3213	2210	1650		5.65 (br s, 2H, N-NH_2), 6.82 (dd, 1H, *J* 3.6, 1.42 Hz, $C_{4'}$-H (furyl)), 7.35 (d, 1H, *J* 3.6 Hz, $C_{3'}$-H (furyl)), 8.08 (d, 1H, *J* 1.42 Hz, $C_{5'}$-H (furyl)), 8.42 (br s, 2H, NH_2).	241 (M^+)
3b	3415 3311	2210	1683 1660		0.94 (t, 3H, *J* 7.16 Hz, CH_3), 3.98 (q, 2H, *J* 7.16 Hz, CH_2), 5.70 (br s, 2H, N-NH_2), 6.72 (dd, 1H, *J* 2.72, 1.64 Hz, $C_{4'}$-H (furyl)), 6.93 (d, 1H, *J* 2.72 Hz, $C_{3'}$-H (furyl)), 7.90 (d, 1H, *J* 1.64 Hz, $C_{5'}$-H (furyl)), 8.30 (br s, 2H, NH_2).	288 (M^+)
4	3408 3292 3280	2183	1710		4.23 (d, 1H, *J* 6.4 Hz, C_4-H), 5.09 (d, 1H, *J* 6.4 Hz, C_3-H), 5.30 (br s, 2H, N-NH_2), 6.32 (dd, 1H, *J* 3.26, 1.8 Hz, $C_{4'}$-H (furyl)), 6.46 (d, 1H, *J* 3.26 Hz, $C_{3'}$-H (furyl)), 6.95 (br s, 2H, NH_2), 7.62 (d, 1H, *J* 1.8 Hz, $C_{5'}$-H (furyl)).	243 (M^+)

Table 2. *Continued on the next page.*

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10a	3120	2204	1650	6.78 (dd, 1H, *J* 3.6, 1.5 Hz, $C_{4'}$-H (furyl)), 7.20 (d, 1H, *J* 3.6 Hz, $C_{3'}$-H (furyl)), 8.01 (d, 1H, *J* 1.5 Hz, $C_{5'}$-H (furyl)), 8.20 (br s, 1H, NH), 8.28 (s, 1H, C_2-H).	251 (M^+)
10b	3120	2214 1650	1691	1.07 (t, 3H, *J* 7.10 Hz, CH_3), 4.08 (q, 2H, *J* 7.10 Hz, CH_2), 6.65 (dd, 1H, *J* 3.52, 1.42 Hz, $C_{4'}$-H (furyl)), 6.82 (d, 1H, *J* 3.52 Hz, $C_{3'}$-H (furyl)), 7.81 (d, 1H, *J* 1.42 Hz, $C_{5'}$-H (furyl)), 8.22 (s, 1H, C_2-H), 8.30 (br s, 1H, NH).	298 (M^+)
11a	3440	2220	1650	2.58 (s, 3H, CH_3), 6.77 (dd, 1H, *J* 3.6,1.50 Hz, $C_{4'}$-H (furyl)), 7.17 (d, 1H, *J* 3.60 Hz, $C_{3'}$-H (furyl)), 7.99 (d, 1H, *J* 1.50 Hz, $C_{5'}$-H (furyl)), 8.21(br s, 1H, NH).	265 (M^+)
11b	3340	2229	1695 1671	1.04 (t, 3H, *J* 7.18 Hz, CH_3-ethyl), 2.53(s, 3H, CH_3), 4.11 (q, 2H, *J* 7.18 Hz, CH_2), 6.74 (dd, 1H, *J* 3.60,1.50 Hz, $C_{4'}$-H (furyl)), 6.91 (d, 1H, *J* 3.60 Hz, $C_{3'}$-H (furyl)), 7.87 (d, 1H, *J* 1.50 Hz,$C_{5'}$-H (furyl)), 7.95 (br s, 1H, NH).	312 (M^+)
12	3461	2225	1738 1707 1674	2.38 (d, 9H, *J* 4.94, $3CH_3$), 6.76 (dd, 1H, *J* 3.60, 1.70 Hz, $C_{4'}$-H (furyl)), 7.09(d, 1H, *J* 3.60 Hz, $C_{3'}$-H (furyl)), 8.00 (d, 1H, *J* 1.70 Hz, $C_{5'}$-H (furyl)), 13.15 (br s, 1H, NH).	367 (M^+)
13a		2215	1685	1.52 (t, 3H, *J* 7.40 Hz, CH_3), 4.51 (q, 2H, *J* 7.40 Hz, CH_2), 6.87 (dd, 1H, *J* 3.60,1.50 Hz, $C_{4'}$-H (furyl)), 7.40 (d,1H, *J* 3.60 Hz, $C_{3'}$-H (furyl)), 8.16 (d, 1H, *J* 1.50 Hz, $C_{5'}$-H (furyl)), 9.27 (s, 1H, C_2-H).	279 (M^+)
13b		2215	1680	1.43 (t, 3H, *J* 6.90 Hz, CH_3-ethyl), 2.70 (s, 3H, CH_3); 4.87 (q, 2H, *J* 6.90 Hz, CH_2), 6.85 (dd, 1H, *J* 3.60, 1.60 Hz, $C_{4'}$-H (furyl)), 7.40 (d,1H, *J* 3.60 Hz, $C_{3'}$-H (furyl)), 8.13 (d, 1H, *J* 1.60 Hz, $C_{5'}$-H (furyl)).	293 (M^+)
13c		2206	1724 1647	1.07 (t, 3H, *J* 7.15 Hz, CH_3, OEt), 1.54(t, 3H, *J* 7.20 Hz, CH_3, NEt), 4.10 (q, 2H, *J* 7.15 Hz, OCH_2), 4.47 (q, 2H, *J* 7.20 Hz, NCH_2), 6.72 (dd, 1H, *J* 3.60, 1.80 Hz, $C_{4'}$-H (furyl)), 6.95 (d, 1H, *J* 3.60 Hz, $C_{3'}$-H (furyl)), 7.90 (d, 1H, *J* 1.80 Hz, $C_{5'}$-H (furyl)), 10.64 (s, 1H, C_2-H).	

Table 2. *Continued on the next page.*

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13d		2204	1701 1664	1.07 (t, 3H, *J* 7.15 Hz, CH_3, OEt), 1.46 (t, 3H, *J* 7.28 Hz, CH_3, NEt), 3.14 (s, 3H, CH_3), 4.10 (q, 2H, *J* 7.15 Hz, OCH_2), 4.42 (q, 2H, *J* 7.28 Hz, NCH_2), 6.71 (dd, 1H, *J* 3.50,1.50 Hz, $C_{4'}$-H (furyl)), 6.94(d, 1H, *J* 3.50 Hz, $C_{3'}$-H (furyl)), 7.88 (d,1H, *J* 1.50 Hz, $C_{5'}$-H (furyl)).	340 (M^+)
14a	3440	2206	1660	1.60 (m, 6H, $3CH_2$, piper.), 3.02 (m, 4H, $2CH_2$, piper.), 6.79 (dd, 1H, *J* 3.50, 1.80 Hz, $C_{4'}$-H (furyl)), 7.21 (d, 1H, *J* 3.50 Hz, $C_{3'}$-H (furyl)), 7.37 (m, 2H, 2CH (aryl)), 8.02 (d, 1H, *J* 1.80 Hz, $C_{5'}$-H (furyl)), 8.22 (m, 4H, 2CH (aryl), NH_2).	345 (M^+ - piper.)
14b	3440	2212	1646	1.64 (m, 6H, $3CH_2$, piper.), 3.02 (m, 4H, $2CH_2$, piper.), 6.83 (dd, 1H, *J* 3.42, 1.80 Hz, $C_{4'}$-H (furyl)), 7.06 (m, 2H, 2CH (aryl)), 7.28 (d, 1H, *J* 3.42 Hz, $C_{3'}$-H (furyl)), 7.43 (m, 1H, CH (aryl)), 8.11 (m, 2H, $C_{5'}$-H (furyl), CH (aryl)), 8.26 (br s, 2H, NH_2), 11.29 (br s, 1H, OH).	343 (M^+ - piper.)
14c	3446	2210	1710 1650	1.10 (t, 3H, *J* 7.02 Hz, CH_3); 1.62 (m, 6H, $3CH_2$, piper.), 3.01 (m, 4H, $2CH_2$, piper.), 4.12 (q, 2H, *J* 7.02 Hz, CH_2), 6.67 (dd, 1H, *J* 3.60, 1.50 Hz, $C_{4'}$-H (furyl)), 6.82 (d, 1H, *J* 3.60 Hz, $C_{3'}$-H (furyl)), 7.35 (m, 2H, 2CH (aryl)), 7.82 (d, 1H, *J* 1.50 Hz, $C_{5'}$-H (furyl)), 8.18 (m, 2H, 2CH (aryl)), 8.30 (br s, 2H, NH_2).	392 (M^+ - piper.)
14d	3415	2210	1700 1660	1.15 (t, 3H, *J* 7.12 Hz, CH_3), 1.60 (m, 6H, $3CH_2$, piper.), 3.02 (m, 4H, $2CH_2$, piper.), 4.14 (q, 2H, *J* 7.12 Hz, CH_2), 6.67 (dd, 1H, *J* 3.36, 1.50 Hz, $C_{4'}$-H (furyl)), 6.84 (d, 1H, *J* 3.36 Hz, $C_{3'}$-H (furyl)), 7.00 (m, 2H, 2CH (aryl)), 7.37 (m, 1H, CH (aryl)), 7.84 (d, 1H, *J* 1.50 Hz, $C_{5'}$-H (furyl)), 8.10 (m, 1H, CH (aryl)), 8.24 (br s, 2H, NH_2), 12.10 (br s, 1H, OH).	390 (M^+ - piper.)
15a	3448	2216	1650	6.79 (dd, 1H, *J* 3.60, 1.50 Hz, $C_{4'}$-H (furyl)), 7.21 (d, 1H, *J* 3.60 Hz, $C_{3'}$-H (furyl)), 7.37 (m, 2H, 2CH (aryl)), 8.02(d, 1H, *J* 1.50 Hz, $C_{5'}$-H (furyl)), 8.23 (m, 2H, 2CH (aryl)).	

Table 2. *Continued on the next page.*

Table 2. *Continued from the previous page.*

15b	3440	2218	1650		6.81 (dd, 1H, *J* 3.36, 1.50 Hz, $C_{4'}$-H(furyl)), 7.03 (m, 2H, 2CH (aryl), 7.27 (d, 1H, *J* 3.36 Hz, $C_{3'}$-H (furyl)), 7.41 (m, 1H, CH (aryl)), 8.04 (d, 1H, *J* 1.50 Hz, $C_{5'}$-H (furyl)), 8.10 (m, 1H, CH (aryl)).	343 (M^+)
15c	3440	2224	1703 1654		1.07 (t, 3H,*J* 7.12 Hz, CH_3), 4.13 (q, 2H, *J* 7.12 Hz, CH_2), 6.71 (dd, 1H,*J* 3.38, 1.60, $C_{4'}$-H (furyl)), 6.90 (d, 1H, *J* 3.38 Hz, $C_{3'}$-H (furyl)), 7.43 (m, 2H, 2CH (aryl)), 7.89 (d, 1H, *J* 1.60 Hz, $C_{5'}$-H (furyl)), 8.23 (m, 2H, 2CH (aryl)).	392 (M^+)
15d	3365	2225	1730 1647		1.13 (t, 3H, *J* 7.08 Hz, CH_3), 4.14 (q,2H, *J* 7.08 Hz, CH_2), 6.71 (dd, 1H, *J* 3.36,1.70 Hz, $C_{4'}$-H (furyl)), 6.88 (d, 1H, *J* 3.36 Hz, $C_{3'}$-H (furyl)), 7.06 (m, 2H, 2CH, (aryl)), 7.47 (m, 1H, CH, (aryl)), 7.89 (d, 1H, *J* 1.70 Hz, $C_{5'}$-H (furyl)), 8.09 (m, 1H, CH, (aryl).	390 (M^+)
17b	3441 3291	2214	1694 1650		0.93 (t, 3H, *J* 7.10 Hz, CH_3), 3.95 (q, 2H, *J* 7.10 Hz, CH_2), 6.72 (dd, 1H, *J* 3.60,1.60 Hz, $C_{4'}$-H (furyl)), 6.92 (d, 1H, *J* 3.60 Hz, $C_{3'}$-H (furyl)), 7.56 (br s, 2H, NH_2), 7.89 (d, 1H, *J* 1.60 Hz, $C_{5'}$-H (furyl)), 11.66 (br s, 1H, OH).	273 (M^+)
24a	3357 3280	2204		1220	6.79 (dd, 1H, *J* 3.56, 1.74 Hz, $C_{4'}$-H (furyl)), 7.45 (d, 1H, *J* 3.56 Hz, $C_{3'}$-H (furyl)), 8.02 (d, 1H, *J* 1.74 Hz, $C_{5'}$-H (furyl)), 8.28 (br s, 2H, NH_2), 12.95 (br s, 1H, SH).	258 (M^+)
24b	3435 3280 3200		1711	1241	1.29 (t, 3H, *J* 7.10 Hz, CH_3), 4.28 (q, 2H, *J* 7.10 Hz, CH_2), 6.69 (dd, 1H. *J* 3.56,1.70 Hz, $C_{4'}$-H (furyl)), 7.43 (d, 1H, *J* 3.56 Hz, $C_{3'}$-H (furyl)), 7.90 (d, 1H, *J* 1.70 Hz, $C_{5'}$-H (furyl)), 8.03 (br s, 2H, NH_2), 12.83 (br s, 1H, SH).	305 (M^+)

* NH_2, OH and SH groups are D_2O-exchangeable.

Experimental

Melting points are uncorrected. Microanalyses were done in the Microanalytical Laboratory, National Research Centre, Cairo, Egypt. IR spectra (KBr disc) were recorded using a Jasco FT/IR-300E spectrophotometer. ^{1}H NMR spectra were recorded in DMSO-d_6 using Varian Mercury 300 MHz and Varian Gemini 200 MHz. The chemical shifts are reported in δ relative to Me_4Si. Mass spectra were recorded on GC/MS Finnigan SSQ 7000 spectrometer.

1,6-Diamino-4-(2-furyl)-2-oxo-1,2-dihydropyridine-3,5-dicarbonitrile (3a) and 1,6-diamino-4-(2-furyl)-2-oxo-1,2,3,4-tetrahydropyridine-3,5-dicarbonitrile (4). A mixture of **1** (1 g, 0.01 mol) and **2a** (1.44 g, 0.01 mol) in absolute ethanol (20 mL) was heated under reflux for 3 h. The precipitated product was filtered off and purified by crystallization from *n*-butanol to give **3a** (1.45 g, yield 60%, Tables 1 and 2). When the mother liquor of the reaction was thermally concentrated and left to cool, another crop of a solid product was obtained (which was crystallized from ethanol) and identified as product **4** (0.32 g, 13%).

Dehydrogenation of 4 to 3a. To a suspension of **4** (0.24 g, 1 mmol) in dry diethyl ether (30 mL) was added *o*-chloranile (1 mmol). The reaction mixture was stirred at room temperature (~25 °C) for 2 h. The solid product obtained was filtered off, washed with diethyl ether and crystallized from *n*-butanol to give **3a** (0.2 g, 84% yield).

Ethyl 5-cyano-1,2-diamino-4-(2-furyl)-6-oxo-1,6-dihydropyridine-3-carboxylate (3b). A mixture of **1** (1g, 0.01 mol) and **2b** (1.91 g, 0.01 mol) in absolute ethanol (20 mL) containing triethylamine (0.5 mL) was heated under reflux for 4 h and the reaction mixture was left to cool. The solid product obtained was filtered off and crystallized for purification from ethanol to give **3b** (1.73 g, 60%).

Reaction of 3a and 3b with ethyl chloroformate/DMF reagent mixture. To a mixture of ethyl chloroformate/N,N-dimethylformamide (30 mL, 1:5) compound **3a** or **3b** (0.01 mol) was added and the reaction mixture was heated under reflux for 3 h. The reaction mixture was evaporated to dryness under reduced pressure and the residue was triturated with MeOH (5 mL). The solidified material was filtered off, washed several times with MeOH and then crystallized for purification from the proper solvent to give **10**.

7-(2-Furyl)-2-methyl-5-oxo-3,5-dihydro[1,2,4]triazolo[1,5-*a*]-pyridine-6,8-dicarbonitrile (11a) and N-acetyl-N-[6-(acetylamino)-3,5-dicyano-4-(2-furyl)-2-oxopyridin-1(2H)-yl]acetamide (12). A mixture of **3a** (0.5 g) and acetic anhydride (15 mL) was heated under reflux for 5 h. The solid product obtained was filtered off and

crystallized from acetonitrile to give **11a** (0.18 g, 33% yield). When the mother liquor of the reaction was evaporated till dryness under reduced pressure an oily residue was obtained which solidified upon trituration with ethyl acetate. The solid obtained was filtered off and crystallized from methyl alcohol to give **12** (0.11 g, 15% yield).

Ethyl 5-cyano-7-(2-furyl)-2-methyl-5-oxo-3,5-dihydro[1,2,4]triazolo-[1,5-*a*]-pyridine-8-carboxylate (11b). A mixture of **3b** (0.5 g) and acetic anhydride (15 mL) was heated under reflux for 5 h. The reaction mixture was then evaporated to dryness under reduced pressure. The obtained residue solidified when triturated with MeOH. The solid product was filtered off, washed with MeOH and then crystallized from *n*-butanol to give **11b** (0.31 g, 57% yield).

General Procedure for the Synthesis of 3-ethyl[1,2,4]triazolo[1,5-*a*]pyridine derivatives 13:

Method A:

A mixture of **3a** or **3b** (0.01 mol) and triethyl orthoformate or triethyl orthoacetate (0.02 mol) in acetonitrile (50 mL) was heated under reflux for 5-10 h. The reaction mixture was then evaporated to dryness under reduced pressure, and the obtained residue was triturated with methyl alcohol. The obtained solid product was filtered off and crystallized from the appropriate solvent to give **13** (Table 1).

Method B:

A mixture of **10** or **11** (0.01 mol) and triethyl orthoformate or triethyl orthoacetate (0.03 mol) in acetonitrile (20 mL) was heated under reflux for 5-10 h. The reaction mixture was evaporated to dryness under reduced pressure. The obtained residue was treated with methanol. The solid product was filtered off and crystallized from the appropriate solvent to give **13**. Product (yield, reaction time): **13a** (73%, 10 h), **13b** (72%, 5 h), **13c** (69%, 10 h), and **13d** (70%, 5 h).

Reaction of 3a and 3b with aldehydes. A mixture of **3a** or **3b** (0.01 mol) and the desired aldehyde (0.01 mol) in 1,4-dioxane (50 mL) containing piperidine (1 mL, 0.012 mol) was heated under reflux for 3 h and then left to cool. The solid product obtained (for products **14c** and **14d** the reaction mixture was evaporated to dryness under reduced

pressure and then treated with methanol) was filtered off and crystallized for purification from the appropriate solvent to give **14**.

Treatment of products 14 with trifluoroacetic acid. A suspension of **14** (0.2 g) in trifluoroacetic acid (5 mL) was stirred at room temperature (~25 °C) for 5 min and then poured into cold water. The solid product obtained was filtered off and crystallized from the appropriate solvent to give **15**.

Reaction of products 3a and 3b with nitrous acid. To a suspension of **3a** or **3b** (0.01 mol) in aqueous acetic acid (100 mL, 60%), sodium nitrite (0.015 mol in 5 mL water) was added. The resulting mixture was stirred at room temperature (~25 °C) for 2 h and then left over night. The solid product obtained was filtered off, washed with water several times and crystallized to give **17**.

6-Amino-2-oxo-1,2-dihydropyridine-3,5-dicarbonitrile 17a: 85% yield, mp 340-42 °C (lit.[27] 45% yield, mp 340 °C).

2-Methyl[1,2,4]triazolo[1,5-*a*]pyridines 11a and b. A mixture of **19** (0.01 mol) and **2a** or **2b** (0.01 mol) in absolute ethanol (30 mL) containing triethylamine (0.5 mL) was heated under reflux for 5-10 h. The reaction mixture was evaporated to dryness under reduced pressure. Trifluoroacetic acid was added to the resulting oil and the solution was poured into cold water. The resulting solid material was filtered off and crystallized to give **11a** (0.80 g, 30% yield, 5 h) or **11b** (1.25 g, 40% yield, 10 h).

Synthesis of 5-amino-7-(2-furyl)-2-thioxo-1,2-dihydropyrano[2,3-*d*]imidazole-6-carbonitrile (24a) and –6-ethyl carboxylate (24b). A mixture of **20** (0.01 mol) and **2a** or **2b** (0.01 mol) in absolute ethanol (30 mL) containing triethylamine (0.5 mL) was heated under reflux for 5-10 h. Then the reaction mixture was concentrated and left to cool. The solid obtained was filtered off and crystallized from the proper solvent to give **24** (Tables 1 and 2).

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Povzetek

Opisana je sinteza diaminopiridinskih derivatov **3** in **4** iz 2-cianoacetohidrazida **1**. Pri reakciji **3** z etil kloroformat/DMF reagentom, acetanhidridom, trietil ortoformatom, -ortoacetatom ali aromatskimi aldehidi smo dobili [1,2,4]triazolo[1,5-*a*]piridinske derivate **10, 11** in **13-15**. Deaminiranje **3** je dalo aminopiridine **17**. Triazolopiridini **11** so nastali tudi v enostopenjski sintezi iz **2** in N′-acetil-2-cianoacetohidrazida **19**. Kondenzacija **20** z **2** je vodila do nastanka pirano[2,3-*d*]imidazolov **24**.